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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,479	05/10/2006	Steffen Goletz	GULDE-63	4918
23599	7590	06/27/2007	EXAMINER	
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			GUSSOW, ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/540,479	GOLETZ ET AL.
	Examiner Anne M. Gussow	Art Unit 1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 77-86 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 77-86 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 23 June 2005 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 6/23/05 and 9/20/06.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application
- 6) Other: _____.

DETAILED ACTION

1. Claims 1-76 have been cancelled.
2. Claims 77-86 have been added and are under examination.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on January 23, 2003. It is noted, however, that applicant has not filed a certified copy of the priority application as required by 35 U.S.C. 119(b).

The certified copy of the priority document must be accompanied by a certified English translation if the priority document was not filed in the English language.

Since the priority document has not been received, the claims receive the priority date of January 23, 2004 for art rejection purposes.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on June 23, 2005 and September 20, 2006 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Drawings

5. The drawings are objected to because the labels on the figures are in German. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to

the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In addition to Replacement Sheets containing the corrected drawing figure(s), applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Sheets" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d)(1). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Specification

6. The abstract of the disclosure is objected to because of the use of legal phraseology. Correction is required. See MPEP § 608.01(b).
7. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

8. The disclosure is objected to because of the following informalities: the specification is not in the preferred order of layout.

Appropriate correction is required.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.

- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

9. The use of the trademarks HiTrap™, Centriprep™, and Maxisorp™ have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademark symbols have not been included in the specification.

10. Claims 84-86 are drawn to the use of a recognition molecule, for the purpose of this office action these claims are being interpreted as a method of using a recognition molecule. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 82 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a.) Claim 82 recites the limitation "the construct according to claim 81" in line 1.

There is insufficient antecedent basis for this limitation in the claim.

b.) Claim 83 recites the limitation "constructs according to claim 77" in lines 1-2.

There is insufficient antecedent basis for this limitation in the claim.

c.) Claims 84-86 provide for the use of a recognition molecule, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. For the purpose of this office action these claims have been interpreted as a method of using a recognition molecule.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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14. Claims 77-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising a CDRH1, CDRH2 and CDRH3 and framework sequences and a method for detecting MUC-1 in cell lines, does not reasonably provide enablement for a recognition molecule comprising only 3 CDRs in the heavy chain, or combinations of sequences of SEQ ID Nos. 33 and 35 or a method of preventing, diagnosing, or treating tumor disease and/or metastasis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a recognition molecule, characterized in that it comprises an amino acid sequence which contains (i) the amino acid sequence SEQ ID No. 1 or 2 and (ii) the amino acid sequence SEQ ID Nos. 3 or 4 and (iii) the amino acid sequence SEQ ID No. 5 or 6 and specifically binds the glycosylated MUC1 tumor epitope, wherein the recognition molecule comprises a combination of sequences SEQ ID Nos. 33 and 35 (variable heavy chain sequences) or humanized variants of said

sequences, wherein the recognition molecule comprises a single chain antibody fragment, a multibody, a Fab fragment, a fusion protein of an antibody fragment with peptides or proteins and/or an Immunoglobulin of the IgG, IgM, IgA, IgE, IgD isotypes and/or subclasses thereof, wherein the recognition molecules are fused, chemically coupled, covalently or non-covalently associated with (i) immunoglobulin domains of various species, (ii) enzyme molecules, (iii) interaction domains, (iv) domains for stabilization, (v) signal sequences, (vi) fluorescent dyes, (vii) toxins, (viii) catalytic antibodies, (ix) one or more antibodies or antibody fragments with different specificity, (x) cytolytic components, (xi) immunomodulators, (xii) immunoeffectors, (xiii) MHC class I or class II antigens, (xiv) chelating agents for radioactive labeling, (xv) radioisotopes, (xvi) liposomes, (xvii) transmembrane domains, (xviii) viruses and/or (xix) cells. The claims are also broadly drawn to a use of a recognition molecule in the prophylaxis, prevention, diagnosis, reduction, therapy, follow-up and/or aftercare of tumor diseases and/or metastasis.

The specification discloses an antibody comprising the CDRs of either SEQ ID Nos. 1, 3 and 5 or 2, 4, and 6 in the heavy chain that binds to the MUC-1 tumor antigen. The specification discloses the heavy chain framework sequences of SEQ ID No. 32 and the light chain framework sequences of SEQ ID No. 34. The specification also discloses a method of detecting MUC1 in tumor cell lines using the antibody. The specification does not disclose an antibody with fewer than 3 CDRs of the heavy chain and 3 CDRs of the light chain. The specification does not disclose preventing, treating, or diagnosing tumor diseases.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci, 1982, Vol. 79, page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. (Journal of Molecular Biology, 1996, Vol. 262, pages 732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Pascalis et al. (Journal of Immunology,

2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (BBRC, 2003. Vol. 307, pages 198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428), additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm et al (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et

al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

Regarding the prevention, diagnosis, and/or treatment of tumor disease, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of

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cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, Vol. 12, page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, both the treatment of just any cancer and/or metastasis in a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News

Services, "Mixed results on new cancer drug", November 9, 2000). Further, Gura (Science, 1997. Vol. 278, pages 1041-1042) discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Lastly, with regards to the prevention of metastasis, the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent metastasis. Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing

workable examples which are not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Therefore, in view of the teachings above and the lack of guidance and/or exemplification in the specification, undue experimentation would be required to produce the claimed recognition molecule and practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce and use the claimed recognition molecule and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for preventing, treating, or diagnosing tumor diseases and/or metastasis, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 101

15. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

16. Claims 77-82 and 84-86 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

a.) Claims 77-82, as written, do not sufficiently distinguish over recognition molecules as they exists naturally because claims 77-82 do not particularly point out any non-naturally occurring differences between the claimed recognition molecules and binding compositions and the structure of naturally occurring antibodies or recognition molecules.

In the absence of the hand of man, the naturally occurring recognition molecules

are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

b.) Claims 84-86 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Conclusion

17. No claims are allowed.

18. Claims 77-86 are free of the prior art. The closest prior art is Madiyalakan (US PG PUB 2002/0132771, published September 19, 2002). Madiyalakan teaches therapeutic compounds comprising antibodies that bind to the tumor associated antigen MUC1. Madiyalakan does not teach nor reasonably suggest a recognition molecule comprising the sequences of SEQ ID Nos. 1, 3 and 5 or 2, 4, and 6.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow, Ph.D.

June 13, 2007



LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER